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Subject: Briefing Document for Arthritis Advisory Committee
Infliximab (Remicade®) and Congestive Heart Failure

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Background

Several lines of experimental evidence support a potential role of TNF-α in the pathogenesis of congestive heart failure (CHF). Elevated circulating levels of TNF-α have been associated with advanced CHF, and TNF-α has been immunolocalized in cardiac myocytes of explanted hearts from patients with dilated cardiomyopathy and ischemic heart disease. TNF-α is also negatively inotropic *in vivo*, and can produce cardiomyopathy and pulmonary edema in animal models. It has been hypothesized that expression of cytokines such as TNF-α constitutes an adaptive response to myocardial injury, and that TNF-α overexpression may lead to deleterious cardiac remodeling with progressive left ventricular (LV) dysfunction.

Centocor initiated a pilot study to explore the safety and biologic effects of Infliximab in CHF: "A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Pilot Trial Evaluating the Effects of Infliximab (Remicade®) in Patients with Stable Class III or IV Congestive Heart Failure, Protocol C0168T30 ("ATTACH"). This document summarizes the salient findings of the study.

Objectives

Primary Endpoint

The primary objective was to evaluate the effect of Infliximab on clinical status at 14 weeks.

Secondary Endpoints

1. combined risk of death and hospitalization for congestive heart failure (CHF) through Week 14 and 28
2. change in left ventricular ejection fraction (LVEF) at Week 14 and Week 28
3. changes in inflammatory markers (C-reactive protein [CRP], tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6])
4. Physician Global Assessment at Week 14 and 28

Study Design

A multicenter, randomized, double-blind, placebo-controlled trial to assess the effects of Infliximab in patients with stable NYHA Functional Class III or IV CHF. Subjects were to be randomized to infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo. Randomization was 1:1:1. Test agents were administered at three times: 0, 2, and 6 weeks post-randomization. The duration of the study was 28 weeks.

Patient Selection

Inclusion Criteria

- males and females, age ≥18
- stable New York Heart Association (NYHA) Functional Class (FC) III-IV CHF due to systolic dysfunction (stable ≡ no hospitalization for CHF, no change in FC, no receipt of intravenous CHF medication within 2 weeks prior to screening)
- left ventricular ejection fraction (LVEF) ≤ 35% by radionuclide ventriculography

- receiving treatment with a diuretic and an angiotensin converting enzyme (ACE) inhibitor (or angiotensin II antagonist)

Exclusion Criteria

- acute myocardial infarction (MI) or coronary revascularization within 2 months
- hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, congenital heart disease
- resuscitation from sudden cardiac death (SCD) or implantable cardiac defibrillator (ICD) discharge within 3 months
- receipt of non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin, positive inotropic agents other than digoxin, calcium antagonists other than amlodipine for hypertension (HTN) or angina, and class IC or III antiarrhythmic agents other than amiodarone
- treatment with β-blocker, digoxin or spironolactone within 3 months unless ongoing and planned to be continued during the 28 week trial
- chronic or recent infection, HIV positivity, presence of transplanted organ, malignancy within 5 years, lymphoproliferative disease, autoimmune disorder, other serious illness

Study Procedures

Treatment Allocation, Blinding and Treatment

Subjects were allocated to treatment by a central IVRS, and randomized in the order they qualified. The three treatment groups were enrolled concurrently. Unblinded pharmacists on site prepared blinded study agents and were charged with maintaining the blind for other study personnel. Results of assays of inflammatory markers were not provided to the sites.

Eligible patients were randomized in equal proportions to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg, each given as a 2-hour intravenous infusion at Weeks 0, 2, and 6 post-randomization. Infliximab infusions were capped at 1 gram.

Study Monitoring

Subjects were evaluated at baseline, Week 1, 2, 6, 10, 14, 20, and 28 post-randomization. NYHA FC, history, physical exam, patient global assessment, inflammatory markers, serum Infliximab level, adverse events, and concomitant medication use were recorded at baseline and each visit. Chest x-ray, 12-lead electrocardiogram (ECG), routine hematology and chemistry labs, LVEF, Minnesota Living with Heart Failure (MLWHF) questionnaire, and SF-36 health survey were evaluated at baseline, Week 14 and 28.

Study Outcomes

Primary Efficacy Endpoint

The primary endpoint is a “clinical composite score,” to be assessed at Week 14, and defined as **improved**, **unchanged** or **worse**, based on the following:

Clinical Status is **worse** if the subject has:

- died *or*
- been hospitalized for CHF (admitted at least overnight and received IV diuretics, vasodilators, or positive inotropic agents for treatment of CHF) *or*
- worsened NYHA FC *or*
- Patient Global Assessment judged to be moderately or markedly worse

Clinical Status is **improved** if:

- the Clinical Status is not worse *AND*
- NYHA FC at 14 weeks is improved relative to baseline *or*
- Patient Global Assessment is moderately or markedly improved

Clinical Status is **unchanged** if it is neither better nor worse.

The **Patient Global Assessment** represents the patient's subjective assessment of their CHF status compared with Week 0, according to the following categories: markedly improved, moderately improved, mildly improved, unchanged, mildly worse, moderately worse, markedly worse. The **Physician Global Assessment** is an identical measure, but gauged by the physician.

Secondary Efficacy Endpoints

1. combined risk of death and hospitalization for CHF through 14 and 28 weeks
2. Δ LVEF; Week 14 minus baseline; Week 28 minus baseline
3. changes in inflammatory markers, compared with baseline, 2 hours after initial infusion and Week 1, 2, 6, 10, 14, 20, and 28
4. Physician Global Assessment at 14 and 28 weeks

Safety Endpoints

1. adverse events (AEs) through Week 14 and 28
2. change in vital signs (VS) during infusions and for 2 hours thereafter
3. anti-infliximab antibodies at Week 20 and 28
4. anti-double stranded DNA antibody at Week 28
5. change in routine labs and ECG, compared with baseline, at Week 14 and 28

Statistical Plan

The test of statistical significance for the Week 14 clinical composite score was an ordered alternative Cochran Mantel Haenszel Test with scores of 1, 2 and 3 for worse, unchanged, and improved, respectively. This was be performed as a 2-sided test at a 5% level of significance. Also, the numbers of subjects with improved composite score at 14 weeks were assessed using Fisher's Exact Test (2-sided, 5% significance level).

A modified intent-to-treat (ITT) analysis was performed. Subjects who withdrew consent, including consent to use their data, were not included in analyses. For subjects with missing Week 14 data, a last observation carried forward (LOCF) approach was used.

No interim analyses were planned or performed.

Results

Subject Disposition

A total of 150 subjects was enrolled at 32 study sites in the US from August 14, 2000 to April 20, 2001. One subject randomized to 10 mg/kg received 5 mg/kg.

Table 1 Subject Disposition

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
subjects randomized	**49**	**50**	**51**
subjects treated	**48**	**50**	**51**
subjects who discontinued treatment	1 (2.1%)	2 (4.0%)	5 (9.8%)
reason for discontinuation			
AE	1 (2.1%)	1 (2.0%)	4 (7.8%)
withdrawal of consent	0	1 (2.0%)	0
death	0	0	0
other	0	0	1 (2.0%)

Baseline Characteristics

Table 2 provides a summary of baseline demographic characteristics and cardiovascular disease status by treatment group. There was good balance between treatment groups with respect to these factors, with the exceptions of gender (24% females in the placebo group versus 15% in the Infliximab groups) and NYHA FC IV (8% in the high-dose Infliximab group, versus 4% in the other two groups). Of note, there was a trend in favor of lower baseline BP in the Infliximab groups, as well as lower BP in the 10 mg/kg group versus the 5 mg/kg group (mean systolic BP was 116, 113, and 110 in the placebo, 5 mg/kg and 10 mg/kg groups, respectively).

Table 2: Demographics, Baseline Cardiovascular Status and History

	Placebo n=49	Infliximab 5 mg/kg n=50	Infliximab 10 mg/kg n=51	Total (n = 150)
age (mean ± SD)	60±12	62±15	62±13	62±13
range	31 - 81	28 - 85	25 - 85	25 - 85
Race [N (%)]				
Caucasian	43 (87.8)	44 (88)	43 (84.3)	130 (86.7)
Black	4 (8.2)	3 (6)	7 (13.7)	14 (9.3)
Other	2 (4.1)	3 (6)	1 (2)	6 (4)
Male [N (%)]	37 (76)	43 (86)	43 (84)	123 (82)
Weight (kg, mean)	94.6	86.9	85.8	89.0
Vital Signs (mean)				
BPs (mmHg)	116	113	110	113
BPd (mmHg)	67	64	64	65
HR (beats per minute)	70	71	69	70
Duration of CHF (years)	4.6	6	4.3	5.0
Prior Hospitalization for CHF [N (%)]	31 (63)	36 (72)	35 (69)	102 (68)
NYHA Class [N (%)]				
III	47 (96)	48 (96)	47 (92)	142 (95)
IV	2 (4)	2 (4)	4 (8)	8 (5)
LVEF (mean)	24.8%	22.9%	23.7%	23.8%
CHF etiology				
coronary artery disease	31 (63)	30 (60)	36 (71)	97 (65)
non-ischemic cardiomyopathy	18 (37)	20 (40)	15 (29)	53 (35)
chronic stable angina	14 (28.6)	9 (18)	12 (23.5)	35 (23.3)
myocardial infarction	31 (63.3)	25 (50)	34 (66.7)	90 (60)
percutaneous coronary intervention	18 (36.7)	12 (24)	17 (33.3)	47 (31.3)
CABG	24 (49)	20 (40)	17 (33.3)	61 (40.7)
cardiac valve surgery	0 (0)	3 (6)	1 (2)	4 (2.7)

Cardiovascular risk factors are summarized in Table 3. The 5 mg/kg Infliximab group had a lower incidence of diabetes; other factors were well-balanced between treatment groups.

Table 3: Cardiovascular Risk Factors (N [%])

	Placebo n=49	Infliximab 5 mg/kg n=50	Infliximab 10 mg/kg n=51	Total n = 150
diabetes	20 (40.8)	14 (28)	19 (37.3)	53 (35.3)
HTN requiring therapy	33 (67.3)	24 (48)	22 (43.1)	79 (52.7)
current smoker	8 (16.3)	8 (16)	8 (15.7)	24 (16)
prior smoker	22 (44.9)	26 (52)	27 (52.9)	75 (50)

Concomitant Medications

Concomitant medication use was similar across treatment groups (Table 4), although fewer subjects in the 5 mg/kg group were receiving digoxin and beta-blockers at baseline. Overall, 97% of subjects were receiving a diuretic, 81% were receiving an ACE inhibitor, 73% were receiving a beta-blocker, and 38% were receiving an aldosterone antagonist.

Table 4: Concomitant Medication Use

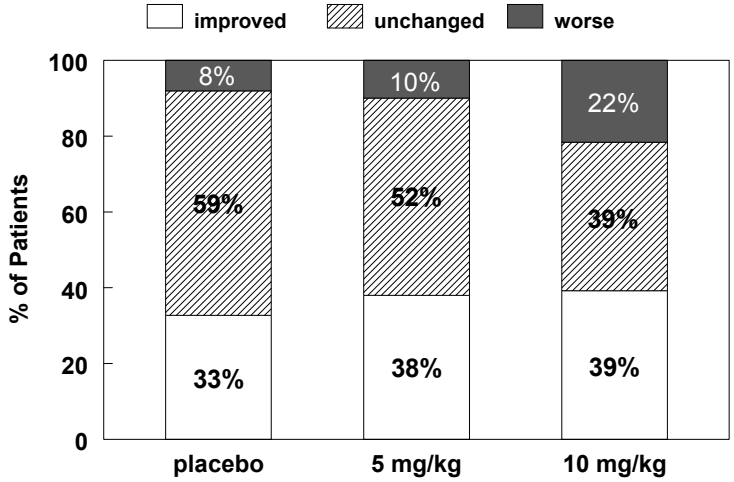
	Placebo n=49	Infliximab 5 mg/kg n=50	Infliximab 10 mg/kg n=51	Total n = 150
digoxin	20 (40.8)	14 (28)	19 (37.3)	53 (35.3)
diuretics	46 (93.9)	49 (98)	50 (98)	145 (96.7)
loop	41 (83.7)	44 (88)	47 (92.2)	132 (88)
aldosterone antagonist	18 (36.7)	23 (46)	17 (33.3)	58 (38.7)
other	12 (24.5)	9 (18)	13 (25.5)	34 (22.7)
beta-blockers	37 (75.5)	32 (64)	41 (80.4)	110 (73.3)
ACE inhibitors	41 (83.7)	40 (80)	41 (80.4)	122 (81.3)
angiotensin II antagonists	12 (24.5)	14 (28)	12 (23.5)	38 (25.3)
calcium channel blockers	7 (14.3)	4 (8)	2 (3.9)	13 (8.7)
nitrates	12 (24.5)	19 (38)	21 (41.2)	52 (34.7)
other vasodilators	2 (4.1)	2 (4)	2 (3.9)	6 (4)
anticoagulant	20 (40.8)	22 (44)	25 (49)	67 (44.7)

Efficacy Results

Primary Efficacy Endpoint: Clinical Status at Week 14

Clinical status is displayed in Figure 1. Slightly greater percentages of subjects in the Infliximab groups showed improvement in clinical status; however, this was offset by a higher percentage of subjects with worse clinical status in the high-dose group. Differences between groups were not statistically significant. Analysis of the individual components of the composite endpoint showed that the trend towards worsening of clinical status in the 10 mg/kg group was driven almost entirely by CHF hospitalizations (8 subjects in the 10 mg/kg group, versus 2 in each of the other two groups). There was also one death in the high-dose group, and no deaths in either of the other groups.

Figure 1: Clinical Status at Week 14



Secondary Endpoints

Left Ventricular Ejection Fraction

Ejection fraction tended to increase in all 3 treatment groups. Over the initial 14 weeks of the study, Δ LVEF was 0.8, 3.5, and 2.1% in the placebo, 5, and 10 mg/kg groups, respectively.

Physician Global Assessment

The physician global assessment at Week 14 was mildly, moderately, or markedly improved in 41% and 45% of evaluated subjects in the low- and high-dose Infliximab groups, respectively, compared to an assessment of improved in 27% of placebo subjects. Four subjects in each group were categorized as mildly worse, one subject in the 10 mg/kg group was classed as moderately worse, and one subject in the high-dose group died. No subjects were assessed as markedly worse.

All-cause mortality or CHF hospitalization

As noted above, there was one death in the 10 mg/kg Infliximab group. Death was attributed to worsening CHF. Rates of all-cause mortality and CHF hospitalization were 4.2 and 4.0% in the placebo and 5 mg/kg Infliximab group, respectively (2 subjects in each group), and 20.9% in the 10 mg/kg Infliximab group (8 subjects).

Other Endpoints

New York Heart Association Functional Class

For subjects who were classified as NYHA FC III at screening (practically all of the study population), approximately 25% were viewed as improved to FC II at Week 14, and there were no notable inter-group differences. One subject in the 10 mg/kg Infliximab group was categorized as FC I. One subject in each of the Infliximab groups declined to FC IV, and one subject in the 10 mg/kg group died.

Patient Global Assessment

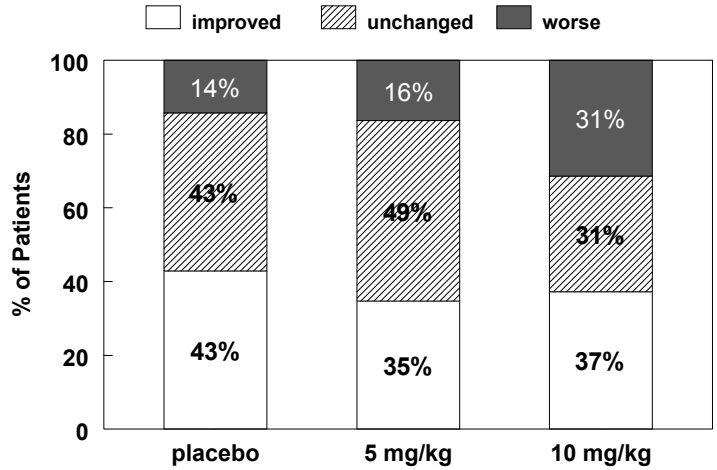
Similar proportions of subjects considered themselves moderately or markedly improved, and the placebo group had the greatest fraction of subjects who considered themselves markedly improved. Generally, more subjects in the Infliximab groups (relative to the placebo group) considered their CHF to be mildly, moderately, or markedly worse.

Salient Endpoints Beyond Week 14

Clinical Status (Week 28)

Week 28 clinical status is summarized in Figure 2. At Week 28, there tended to be fewer subjects with improved clinical statutes and more subjects with worse clinical status in the Infliximab groups relative to the placebo group. The trend toward a deleterious effect was particularly apparent in the 10 mg/kg group, suggesting a dose-response relation between Infliximab and harm.

Figure 2: Clinical Status at Week 28



All-cause mortality or CHF hospitalization (Week 28)

Between Week 14 and Week 28, there were 2 additional deaths in the 10 mg/kg group, and 1 death in the 5 mg/kg group, with no deaths in the placebo group. Mortality rates for the placebo, 5 mg/kg, and 10 mg/kg Infliximab groups were therefore 0%, 2%, and 6%, respectively, through Week 28.

At Week 28, the percentages of subjects hospitalized for CHF were 10.5, 6.0, and 21.6%, and the corresponding rates for all-cause mortality or CHF hospitalization were 10.5, 8.1, and 25.5%.

Physical Exam

Throughout the 28 weeks of the study, there were slight trends toward weight gain in the Infliximab groups, and a slight trend in favor of weight loss in the placebo group. There tended to be higher percentages of subjects with worsened rales and worsened peripheral edema in the Infliximab groups relative to the control group.

All-cause mortality (1 year)

One-year follow-up was complete for all subjects. Deaths and reported cause of death are summarized in Table 5. Mortality rates through one year were 8.2, 8.0, and 15.7% in the placebo, Infliximab 5 mg/kg, and 10 mg/kg groups, respectively. The Kaplan-Meier analysis (not shown) suggests that death tended to occur earlier in both Infliximab-treated groups. The two non-cardiovascular deaths in the 10 mg/kg Infliximab group were attributed to pneumonia and sepsis.

Table 5: All-Cause Mortality Through 1 Year

		Infliximab	
	Placebo (n = 48)	5 mg/kg (n = 50)	10 mg/kg (n = 51)
Deaths	**4 (8.2%)**	**4 (8.0%)**	**8 (15.7%)**
worsening heart failure	**2**	**2**	**3**
arrhythmia	**0**	**1**	**0**
acute MI	**0**	**1**	**1**
other cardiac	**2**	**0**	**2**
non-cardiovascular	**0**	**0**	**2**

Efficacy Summary

Infliximab at doses of 5 mg/kg and 10 mg/kg, administered at 0, 2, and 6 weeks, did not improve clinical status in patients with NYHA FC III and IV CHF. There was increased risk of need for hospitalization for CHF and increased mortality in Infliximab-treated subjects, particularly at the higher dose.

Safety

Deaths

Deaths are briefly described under Efficacy Results, above. For all patients who died, the mode of death was typical of the CHF patient population.

Serious Adverse Events

Through Week 28, cardiac failure was reported as a serious adverse event (SAE) in 44%, 24%, and 8% of subjects in the Infliximab 10 mg/kg, 5 mg/kg, and placebo groups, respectively. Serious adverse events reported in 2 (4%) subjects in the high-dose Infliximab group and in none of the other groups included: increased creatinine phosphokinase, hypotension, myalgia, and myocardial infarction.

Acute Hemodynamic Effects

Of note, Infliximab had acute effects on BP. The proportions of subjects with decreased systolic BP were greater in the 5 mg/kg Infliximab (55%) and 10 mg/kg Infliximab (44%) groups compared with the placebo group (17%). Corresponding decreases in diastolic BP were observed as well: 24%, 18%, and 8%, respectively.

Cardiovascular Adverse Events

Analysis of cardiovascular adverse event rates has the potential to provide clues to help elucidate the mechanism(s) of potentially deleterious action(s) of Infliximab in CHF. Major factors to consider in the CHF patient population include: 1) genesis of arrhythmias; 2) hemodynamic effects; 3) exacerbation of ischemia; and 4) negative inotropism. Adverse events most relevant to CHF are summarized in Table 6.

Table 6: Cardiovascular Adverse Events Through Week 28

		Infliximab	
	Placebo	5 mg/kg	10 mg/kg
	(n = 48)	(n = 51)	(n = 50)
Dizziness	2 (4.2%)	16 (31.4%)	10 (20.0%)
Dyspnea	6 (12.5%)	10 (19.6%)	12 (24.0%)
Cardiac failure	12 (25.0%)	6 (11.8%)	11 (22.0%)
Chest pain	4 (8.3%)	4 (7.8%)	5 (10.0%)
Angina pectoris	1 (2.1%)	3 (5.9%)	4 (8.0%)
Hypotension	0 (0.0%)	3 (5.9%)	4 (8.0%)
Pneumonia	1 (2.1%)	3 (5.9%)	3 (6.0%)
Pulmonary edema	3 (6.3%)	1 (2.0%)	4 (8.0%)
Renal function abnormal	2 (4.2%)	2 (3.9%)	3 (6.0%)
Tachycardia ventricular	4 (8.3%)	2 (3.9%)	3 (6.0%)

There are trends favoring excess dizziness, dyspnea, hypotension, and angina in the Infliximab treatment groups. Of note, dizziness was largely delayed, and not related to the infusion of the agent, per se, despite the apparent acute BP-lowering effect of Infliximab.

Safety Summary

Infliximab was associated with increased risk of death and hospitalization for CHF, as described under Efficacy Results. Consistent with these findings, there are trends favoring excess dizziness, dyspnea, hypotension, angina, and myocardial infarction in the Infliximab treatment groups. The patterns of deaths, physical findings, and adverse events do not suggest a specific mechanism through which Infliximab exerts deleterious effects in patients with CHF.

Summary

ATTACH was a small-sized, multicenter, randomized, double-blind, placebo-controlled dose-ranging, “add-on” study of Infliximab in CHF. The investigation enrolled patients who were NYHA FC III-IV with an EF of $\leq$ 35%. The study failed on its efficacy endpoints, and Infliximab appeared to show harm, as evidenced by excess death and requirement for hospitalization for CHF in the 10 mg/kg group. Although the prespecified

endpoints of death and CHF hospitalization were not increased in the 5 mg/kg Infliximab group, there are clues in the patterns of adverse events that suggest deleterious effects of Infliximab, even at the lower dose. The limited sample size does not make it possible to distinguish between the two doses, and there is no basis to conclude that the 5 mg/kg does not increase mortality.

The study was not designed to assess the effect of Infliximab in milder forms of CHF (NYHA FC I and II), and no conclusions can be drawn regarding the safety of Infliximab in milder forms of CHF.

The patterns of deaths, physical findings, and adverse events do not suggest a unifying mechanism of action leading to harmful effects in the CHF population. The study was too small to provide insight into specific CHF subgroups at particular risk of adverse outcomes with Infliximab.